

arate transplants in 6 patients, and 3 in 1 patient. The percutaneous transhepatic approach was used to gain access to the portal vein into which the islet cells were infused and transported into the liver. The quantity of insulin-producing cells transplanted is approximately double that reported previously.

Not only did the patients have essentially no insulin requirements for the time intervals of follow-up (4.5 to 15.0 months), but they also had no hypoglycemic episodes. The resultant 24-hour blood glucose, insulin requirements, mean amplitudes of glycemic excursions, and percentage of glucose values within normal range are demonstrated in the figure. Toxicity over the short term (up to 15 months) was limited to the requirement for blood transfusions following islet cell infusions (corrected by experience by developing a gel foam pad to be placed with the infusion) and minor superficial ulcerations of the buccal mucosa that resolved after the dose of *sirolimus* was reduced and the capsule formulation of *sirolimus* was substituted for the liquid form. No cytopenia resulting from *sirolimus* was observed. There was effective immunosuppression with no apparent diabetogenic or significant toxic effects, and no evidence of graft rejection, which has been a problem in transplants previously performed utilizing earlier methods and agents.

Shapiro AMJ, et al. *N Engl J Med* 2000;343(4):230-238.

Editor's comment: *This pilot study undoubtedly will lead to other studies that stand a good chance of confirming these rewarding preliminary results. Patient selection was such that the patients were desperately in need of help to control their diabetic symptomatology but had no significant sec-*

ondary complications such as significant renal disease. Hopefully, this procedure will lead to an acceptable and readily available method of treatment for type I diabetic patients regardless of various parameters associated with the basic disease. The utilization of an acceptable nonorgan transplant for adolescents and possibly preadolescents stands a good chance of stabilizing the erratic glucose levels that lead to so many problems in adolescent patients, whose self-images deter them from taking insulin on a regular basis. Endocrinologists are inundated when diabetic patients, for many different reasons, fail to adhere to their treatment regimen. The authors point out that availability of cadaver pancreases is greater than one might think. Fewer than one third of such available pancreases are actually transplanted. Therefore, islet cells can be made available to a significant extent.

The article's concluding paragraph is worth noting: "In patients with type I diabetes, glycemic control can be achieved with intensive insulin therapy and pancreatic transplantation. Intensive insulin therapy does not normalize glycosylated hemoglobin values and may cause severe hypoglycemia. Pancreatic transplantation provides excellent glycemic control, and although the outcome of the procedure has improved dramatically, it remains an invasive procedure with a substantial risk of morbidity. The findings published here indicate that islet transplantation alone is associated with minimal risk and results in good metabolic control with normalization of glycosylated hemoglobin values, and with sustained freedom from the need for exogenous insulin."

Robert M. Blizzard, MD

Hypoglycemia: A Complication of Diabetes Therapy in Children

Because of their erratic activity and eating behavior, hypoglycemia in diabetic children is much more difficult to predict and, therefore, to prevent than pediatricians wish to tolerate. The consequences of hypoglycemia are the greatest in this youngest age group, where these problems are paramount. The authors focus on the whys, the wherefores, and the treatment, since hypoglycemia is the most common acute complication in insulin-treated type I diabetic patients. The younger the patient, the greater the frequency of both mild and severe hypoglycemia. Tighter glycemic control also is associated with increased frequency of hypoglycemia. Conversely, however, people with poor metabolic control whose glycosylated hemoglobin levels are high also are susceptible to severe hypoglycemia. Does hypoglycemia matter? The authors answer with a resounding yes! Symptoms are uncomfortable and carry the fear of loss of control or unconsciousness. Morbidity occurs frequently, and mortality sometimes occurs. In addition, sometimes the patient's fear of hypoglycemia is greater than the fear of future microvascular complications.

Previous and repeated mild hypoglycemia can induce hypoglycemia unawareness, thereby leading to diminished warning symptoms and impaired hormonal counterregulation. The

authors state that even mild hypoglycemia should be considered as having potentially dangerous consequences.

Following this introduction, they discuss the prevalence of hypoglycemia and begin by establishing definitions they believe should be used for "severe hypoglycemia." Some have defined the entity as an event that causes coma or seizures, while others have defined it as any episode that requires external assistance. The authors recommend that severe clinical hypoglycemia should include only episodes of unconsciousness because these can be ascertained consistently across all age groups, which is not possible with a less intense definition. "Mild chemical hypoglycemia" has been defined by some as glucose values below 54 mg/dL but not

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below 40 mg/dL, whereas others use the cutoff glucose level of 65 mg/dL. The authors argue that 60 to 65 mg/dL (3.3 to 3.6 mmol/L) should be used to define "hypoglycemia" whether the patient is symptomatic or not. Unquestionably, severe hypoglycemia is more frequent in adolescents than in adults, as was demonstrated in the diabetes control and complications trial. This was true whether the patients were in the intensive or conventional treatment groups. Data regarding the number of episodes of coma/seizure and also on moderate hypoglycemia per 100 patient-years were considered. The data are well worth reviewing in the original article, particularly by those who deal with diabetes frequently in their practice. The greatest frequency of severe hypoglycemia was found in children <6 years of age. By the fourth year of the study, this group had 42 events per 100 patient-years. This means that of 100 patients having the disease over a 1-year period, there would be 42 severe hypoglycemic episodes.

The authors consider under the causes errors in treating hypoglycemia, the pharmacokinetic and physiologic differences in

children with diabetes, and hypoglycemic unawareness. Considering the consequences, they discuss symptoms, changes in mental efficiency, and chronic brain dysfunction. In considering prevention, they state the key to prevention of severe hypoglycemia and associated complications is prevention of even mild episodes, which requires regular glucose monitoring, and the development of protective strategies on the part of the diabetic patient and family. Insulin regimens and diet and exercise also are considered in this section.

Becker DJ, Ryan CM. *Trends Endocrinol Metab* 2000;11:198-202.

Editor's comment: This article emphasizes the problems of insulin therapy in childhood. It follows the previous abstract (Shapiro et al) because of the potential relationship in future treatment of using islet cell transplants. If the reader has not read this article by Becker and Ryan and is treating children with diabetes, I strongly recommend that he/she do so.

Robert M. Blizzard, MD

Who Wants to Be a Tissue Engineer?

Tissue engineering is a hot topic and not foreign to *GROWTH, Genetics, & Hormones* since many genetic disorders could potentially benefit from regenerated tissues and since tissue regeneration involves local growth and its hormonal control. Successes have been limited in stimulating regeneration of

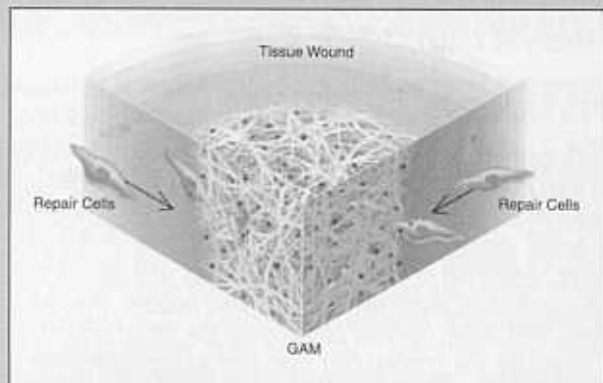
mammalian bone, skin, blood vessel, and spinal cord when bio-material scaffolds, which hopefully might bridge tissues to be regenerated and promote cell migration, proliferation, and differentiation, are used. While attractive, the use of growth factors to enhance regeneration has been hampered by difficulties in selectively delivering potential therapeutic agents at proper concentrations and for extended periods.

Bonadio and coworkers now offer a novel approach to local tissue engineering. The basic concept offered is to introduce plasmid DNA encoding the therapeutic factor into a biodegradable porous scaffold that is implanted into the region where regeneration is desired. The delivery system is called "gene activated matrix," or GAM (Figure 1). As cells grow into the scaffold, they take up the plasmid, express the plasmid DNA, and synthesize the recombinant therapeutic factor. Eventually, the scaffold is degraded as new tissue is formed.

At first glance, this seems too good to be true. However, Bonadio provides evidence that it works. Using wound healing as a model, the group has shown that fibroblasts growing into granulation tissue take up and express recombinant protein for weeks. Referring to earlier work using a canine bone defect model (Figure 2 on page 12), he notes that bone healing is much improved over controls by implantation of GAM-containing plasmids encoding BMP 4 or PTH fragment 1-34, and that the therapeutic effect is enhanced when the 2 plasmids are used together. The results suggest that GAM provides a dose-dependent, reproducible, and safe strategy for stimulating tissue regeneration.

After discussing the rationale for using GAM in wound healing and reviewing experiments with animals, Bonadio turns his attention to how GAM might be used in human medicine. He suggests that the first use of the approach may best be in situ-

Figure 1



The schematic figure shows a GAM implant in a fresh wound site (*inner area*). A GAM at its most basic consists of 2 ingredients: plasmid DNA and a structural matrix carrier. As part of the wound healing response, granulation tissue fibroblasts proliferate and migrate from viable tissue (*outer area*) surrounding the wound into the GAM. Once there, fibroblasts take up and transiently express plasmid DNA. The GAM matrix has 2 functions: It holds plasmid DNA in the wound site (until cells arrive), and it acts as scaffolding that promotes fibroblast ingrowth and accumulation near the DNA. While in the matrix, transfected fibroblasts act as local *in vivo* bioreactors, producing plasmid-encoded proteins that stimulate wound repair.

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